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EFFECTS OF 1, 1-DIMETHYLHYDRAZINE (UDMH) ON EVOKED CEREBRAL NEUROELECTRIC RESPONSES

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FOREWORD

This research was initiated by Toxic Hazards Division, Biomedical Laboratory, Aerospace Medical Research Laboratories, Wright-Patterson Air Force Base, Ohio, under AF 33(615)-2822 with the University of California, Los Angeles, California. The research was performed by Yale University School of Medicine, New Haven, Connecticut for the University of California under Contract SAR/UDMH and supported in part by U. S. Public Health Service Grant M-05286 from the National Institutes of Health. This research supports Project 6302, "Toxic Hazards of Propellants and Materials," and Task 630202, "Pharmacology - Biochemistry." This research started June 1966 and was finished March 1967.

The experiments were performed by W. R. Goff, PhD, and Truett Allison, PhD, both Research Psychologists, Veterans Hospital, West Haven, and Assistant Professors of Psychology (Psychiatry), Yale University School of Medicine, and Y. Matsumiya, PhD, Research Associate, Yale University School of Medicine, New Haven, Connecticut, in collaboration with M. B. Sterman, PhD, and M. D. Fairchild, PhD, Veterans Administration Hospitals, Sepulveda and Long Beach, California and University of California, Los Angeles. Kenneth C. Back, PhD, was contract monitor for the Aerospace Medical Research Laboratories.

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This technical report has been reviewed and is approved.

WAYNE H. McCANDLESS
Technical Director
Biomedical Laboratory
Aerospace Medical Research Laboratories

ABSTRACT

The neural mechanisms of UDMH intoxication have been studied by analyzing changes in cortical, subcortical, and cerebellar neuroelectric potentials evoked by peripheral nerve stimulation. Both chronically implanted and acute, paralyzed unanesthetized cats were used. Results showed that the negative component of the primary somatosensory cortical evoked potential was markedly potentiated by UDMH intoxication while the positive component of this response together with the response from the specific somatic sensory thalamic relay and from the cerebellum were unaffected. The potentiation almost always occurred in the absence of other evoked or spontaneous neuroelectric changes and preceded epileptiform seizure by several minutes. Thus it was usually the sole predictor of seizure. Motor paralysis markedly prolonged seizure onset. These results indicate the UDMH intoxication increases intracortical excitability acting primarily at axo-dendritic synapses to block inhibitory post-synaptic potentials. The resulting positive sensory-motor feedback is an important element in the production of seizures.

SECTION I

INTRODUCTION

The purpose of these studies was to gain a clearer understanding of the neural mechanisms affected by UDMH intoxication. The experiments were carried out in two phases: (1) In freely-moving cats, the behavioral and neurologic effects of 16 and 32 mg/kg UDMH i.p.; and (2) in anesthetized paralyzed cats, the neurologic effects of 64 mg/kg UDMH i.p. The latter experiments were indicated because the violent movements of nonparalyzed animals produce electrical artifacts that obscure evoked response records during seizure and, more important, these experiments provide data relevant to the sensorimotor feedback hypothesis of Fairchild and Sterman (1964).*

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*Fairchild, M. D. and Sterman, M. B., Behavioral and Neurophysiological Studies of UDMH in the Cat, AMRL-TDR-64-72 (AD 608089), Aerospace Medical Research Laboratories, Wright-Patterson Air Force Base, Ohio, September 1964, 21 pp.

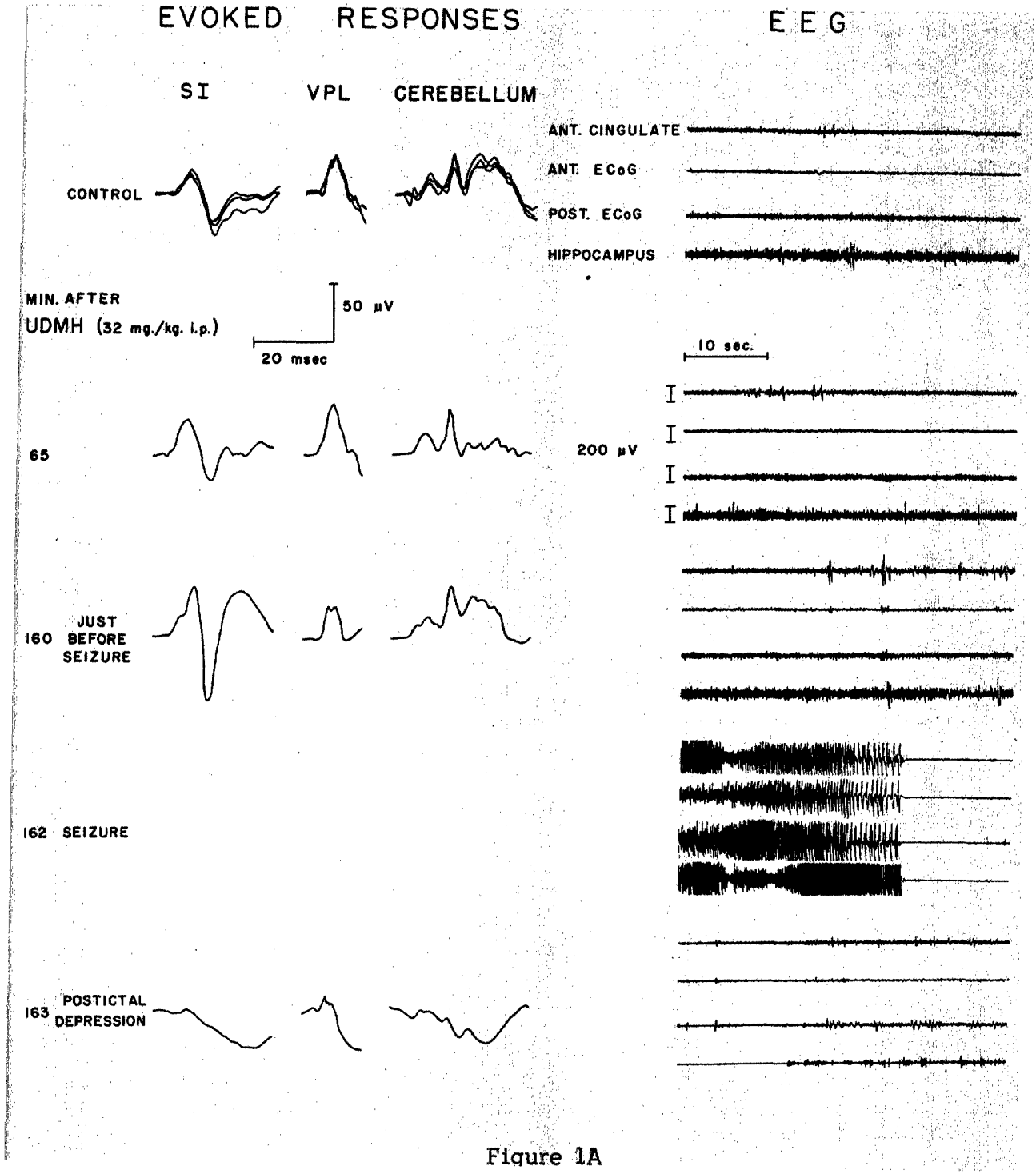

EVOKED RESPONSES
EEG
SI
VPL
CEREBELLUM
ANT. CINGULATE
ANT. ECoG
POST. ECoG
HIPPOCAMPUS
CONTROL
MIN. AFTER
UDMH (32 mg./kg. i.p.)
50 µV
20 msec
10 sec.
65
200 µV
160 JUST BEFORE SEIZURE
162 SEIZURE
163 POSTICTAL DEPRESSION

Figure 1A

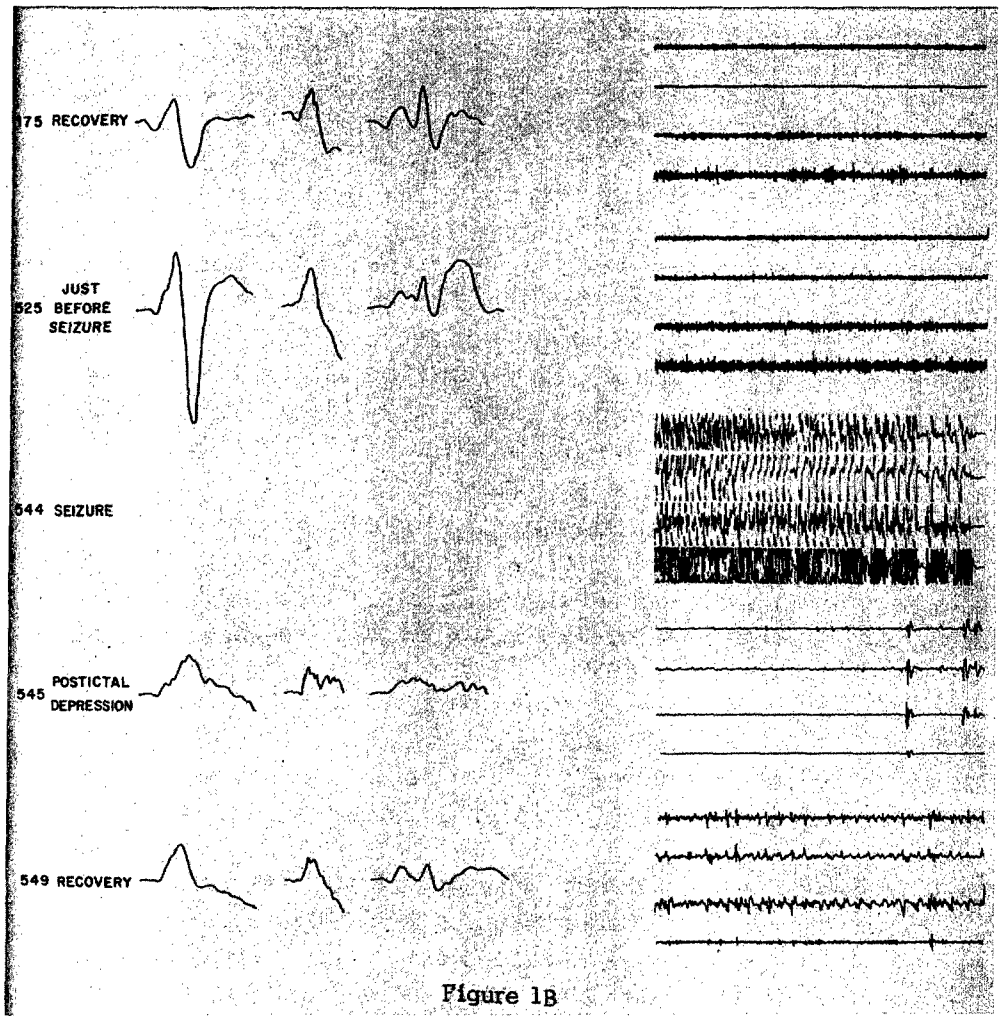


Figure 1B

Electroencephalographic (Right Column) and Average evoked Response (Left Columns) Correlates of UDMH Poisoning in an Awake, Freely-Moving Cat with Implanted Electrodes. Evoked responses are recorded from primary somatosensory cortex (SI), somatosensory thalamic relay nucleus (VPL) and forearm area of the anterior cerebellum. The responses were recorded with reference to a frontal sinus lead, and positive at the active electrode is recorded upward. Each average response consists of 15 individual responses. Blank spaces in evoked response columns indicate times when the response could not be accurately recorded due to paroxysmal EEG activity, movement artifact or both. EEG records during seizure and postictal phases are continuous.

SECTION II

PROCEDURE AND RESULTS

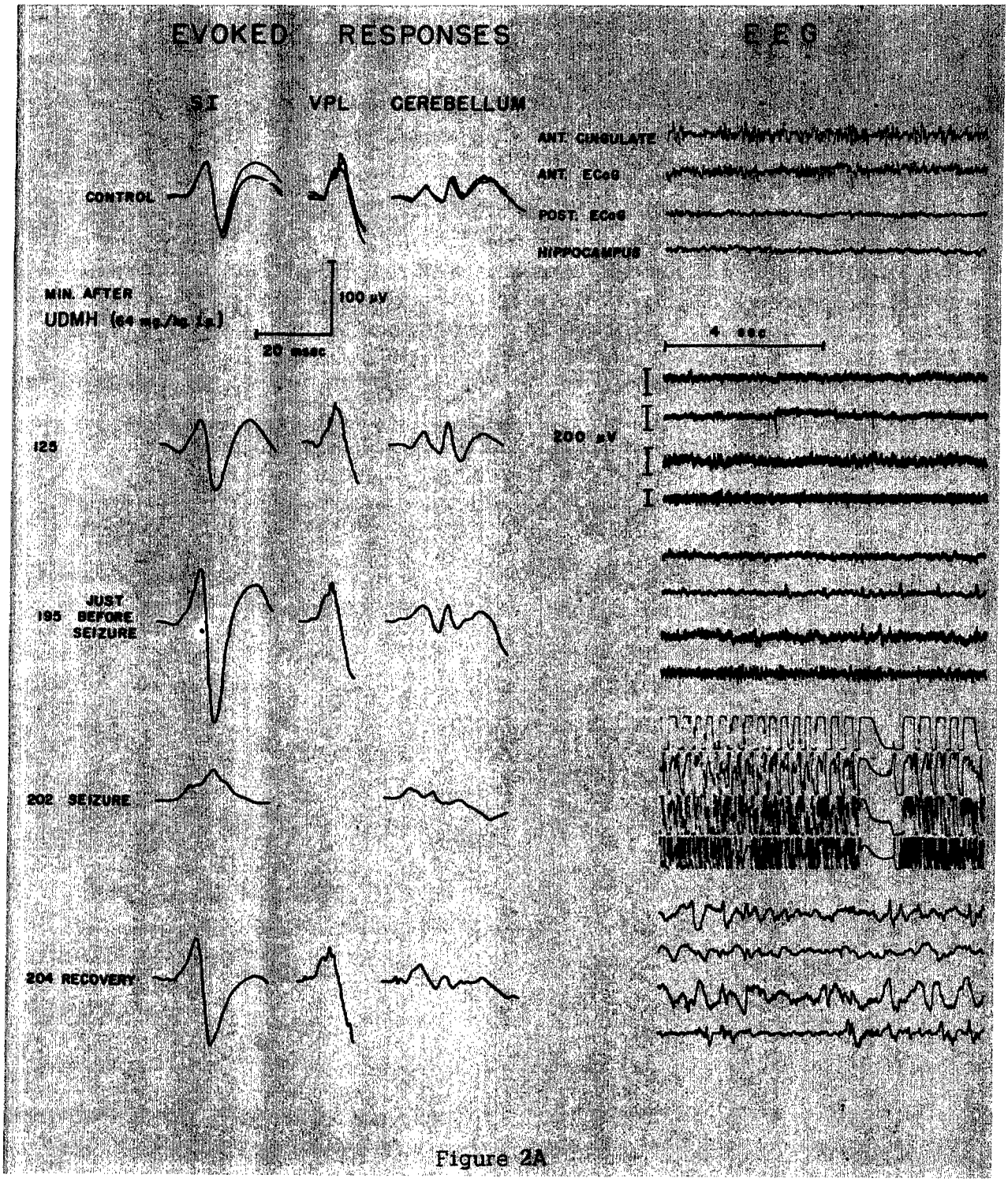
Twelve experiments were carried out on 10 animals prepared with chronic recording electrodes in various areas of the brain, and chronically implanted ulnar nerve stimulating electrodes. Our major findings from experiments in nonparalyzed animals are typified by figures 1A and 1B. Similar results have been obtained in a number of other experiments. This freely-moving, unanesthetized cat was given 32 mg/kg UDMH i.p. For a considerable period of time after UDMH administration, evoked potential amplitudes remained at control levels; the EEG was normal. By 160 minutes after UDMH administration, the negative phase of the primary response of somatosensory cortex (SI) had become extremely large; there is also some enhancement of the primary positive wave, but the thalamic relay nucleus response (VPL) and the response in the forearm representation in the anterior lobe of the cerebellum remained essentially at control levels. All EEG traces at this time were normal. Two minutes later (162 min) the cat went into a full-blown EEG and behavioral convulsion consisting of the usual tonic, clonic, and postictal depression phases. In this experiment it was impossible to record evoked responses during the seizure itself because of the extremely large paroxysmal EEG activity and movement artifacts.

With the exception of the primary positive SI response, the evoked potentials are virtually abolished during the postictal depression phase, but recover in a short time to control levels. With essentially the same sequence of evoked potential changes a second and third seizure ensued. Data for the second seizure are not presented, but as shown in figure 1B, the third seizure was presaged by a potentiated SI negativity at 525 minutes with convulsion occurring at 544 minutes. During the postictal depression all evoked activity is again severely depressed with the exception of the primary positive wave, which appears to be much more resistant to the paroxysmal neural events of the seizure and postictal phases. Immediately after the third convulsion the animal was sedated with Nembutal.®

Eight days later this animal was tracheotomized and venous cannulated under halothane, immobilized with Flaxedil® and maintained on forced respiration. Wound margins were locally anesthetized with Xylocaine,® and the halothane was removed and its effects allowed to wear off. Evoked responses and EEG recordings were made as before. The animal was given 64 mg/kg UDMH i.p. The results are shown in figures 2A and B. Again, the only precursor of the first convulsion was

an extreme augmentation of the SI primary negativity. The EEG at this time was not perceptibly abnormal. At the beginning of the tonic-clonic phase of the seizure the SI response remained large, but was abolished during the second half of the seizure. Note that the VPL and cerebellar responses did not potentiate before the seizure. After the seizure the SI response quickly became abnormally large again, and the sequence of events before, during, and following the second seizure (fig 2B) was very much like that of the first seizure. Two additional seizures, not shown in figure 2, gave very similar results.

The limbic system in both man and animals is particularly prone to seizure activity. Fairchild and Sterman (1964) have previously suggested that UDMH-induced convulsions originate in the limbic system and then spread to the cerebral cortex. Two examples of such a progression, observed in the present investigation, are presented in figures 3A and B. These records are perhaps the clearest we have obtained, but similar results have been seen in several other animals. Seizure activity begins in the anterior cingulate gyrus and hippocampus, with minimal or no involvement of cerebral cortex until several seconds later. The examples shown here were "subseizures" with few or no behavioral concomitants. In both cases the EEG returned briefly to normal following this seizure activity, but within 2 minutes a full EEG and behavioral convulsion ensued.


EVOKED RESPONSES
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SI
VPL
CEREBELLUM
CONTROL
MIN. AFTER
UDMH (64 mg./kg. i.p.)
100 μV
20 msec
125
195 JUST BEFORE SEIZURE
202 SEIZURE
204 RECOVERY
ANT. CINGULATE
ANT. ECoG
POST. ECoG
HIPPOCAMPUS
4 sec
200 μV

Figure 2A

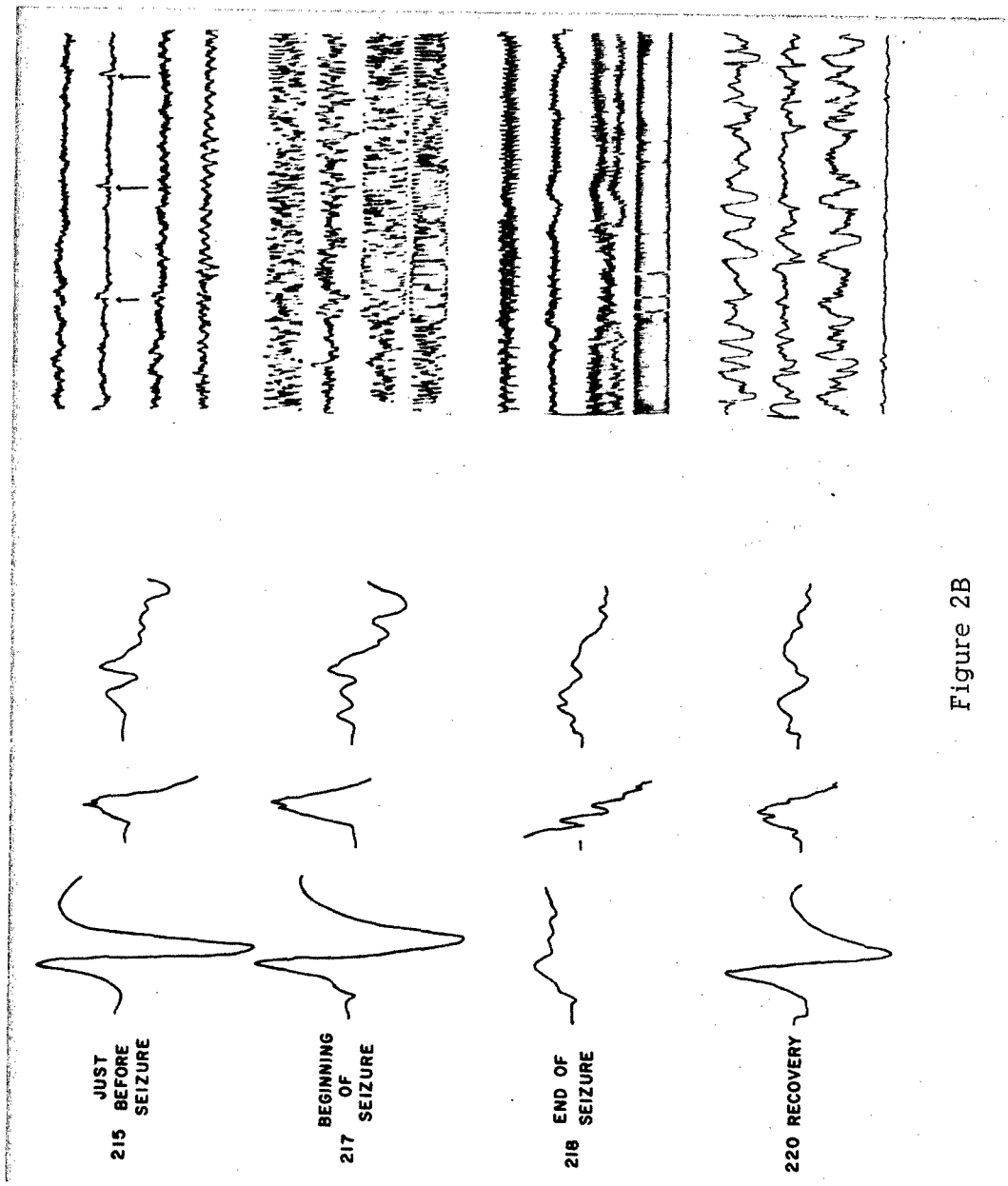

Figure 2B

Electroencephalographic (Right Column) and Average Evoked Response (Left Columns) Correlates of UDMH Poisoning in the Cat (Fig 1, 8 Days Later) Immobilized with Flaxedil and Artificially Respirated. EEG and evoked response recordings same as in Figure 1.

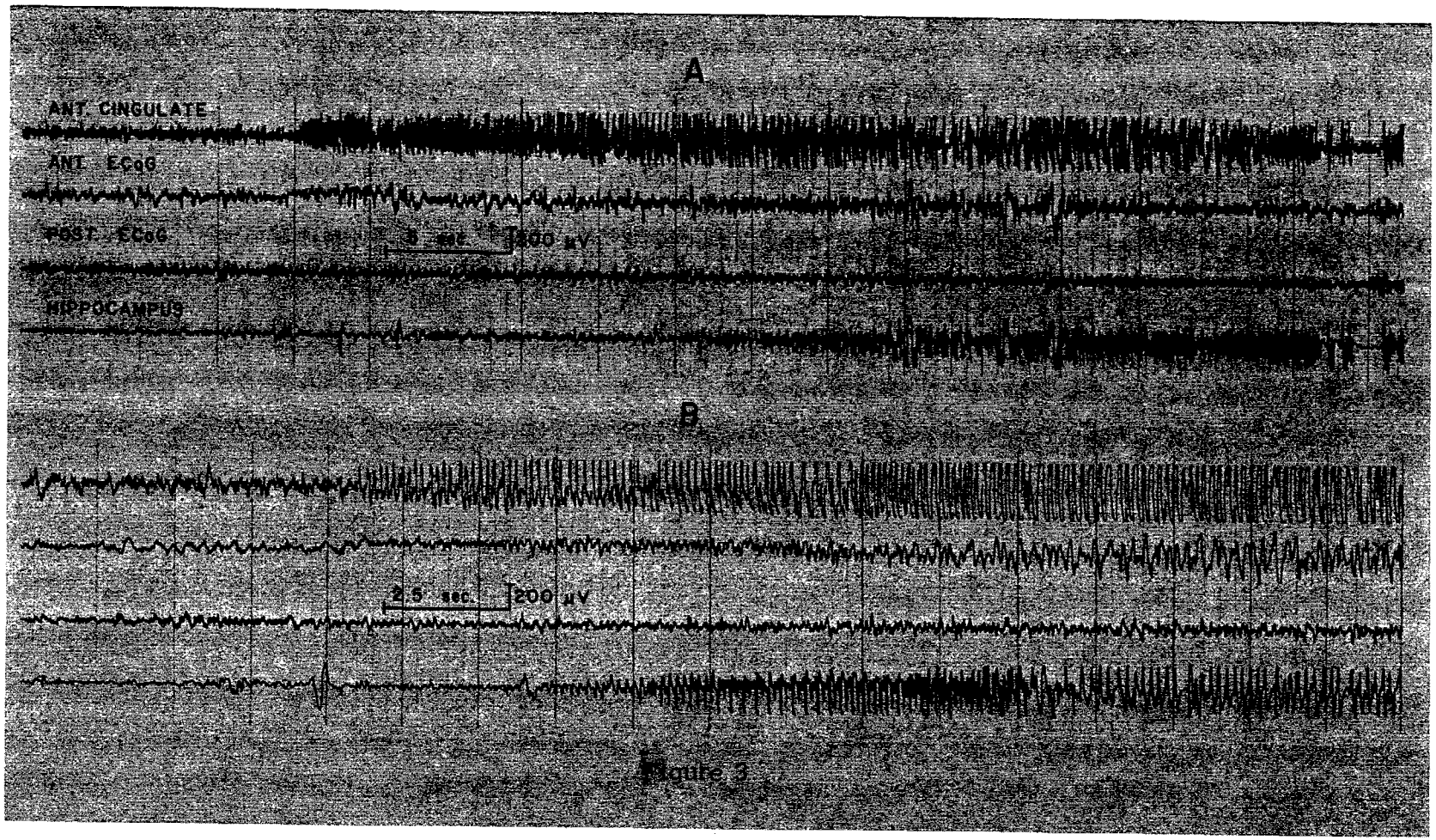
A
ANT. CINGULATE
ANT. ECoG
POST. ECoG
HIPPOCAMPUS
5 sec.
1000 μV
B
2.5 sec.
200 μV

Figure 3

SECTION III

CONCLUSIONS

The following tentative conclusions and interpretations are drawn from these results.

Perhaps the most dramatic finding of this study is that cortical evoked response recordings predict when seizure will occur. When the primary SI negativity becomes exceedingly large it is probable that a seizure will follow within a few minutes. We emphasize that the EEG record and behavior preceding a seizure are usually within normal limits. Thus, the amplitude of the primary negativity is a sensitive, reliable, and, so far as we know, sole, predictor of a seizure. Indeed this has proven very useful in practice because it allows the experimenters to mobilize themselves and the experimental apparatus to cope with the fast-moving events of the seizure, postictal, and recovery phases of the experiment.

In terms of underlying neural mechanisms, the extremely large response of the somatosensory cortex before a seizure is not due to an increase in sensory inflow to the cortex, because the VPL response, which represents the output of the somatosensory relay nucleus in the thalamus, is in our experience within normal (control) limits before a seizure. Thus, UDMH appears to increase intracortical neural excitability. We may further conclude that the drug acts primarily at axodendritic synapses, as it is known that the SI negativity is due to activation of synapses on the dendrites of somatosensory cortex pyramidal cells. The SI negativity is due to activation of synapses on the dendrites of somatosensory cortex pyramidal cells. The SI positivity which is much less affected by UDMH is, on the other hand, due to axo-somatic activation. We also reason that UDMH acts in some manner by blocking inhibitory posesynaptic potentials because is has little effect on cerebellar evoked responses before a seizure. Purpura et al. (1959)* have shown that there are relatively few inhibitory synapses in the cerebellum. If UDMH exerted its effect by enhancing excitatory postsynaptic potentials, cerebral and cerebellar cortex responses should be affected. Thus, UDMH (or its active metabolic by-product) must be an inhibitory synapse blocking agent.

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*Purpura, D. P., Girado, M., and Grundfest, H., "Synaptic Components of Cerebellar Electrocortical Activity Evoked by Various Afferent Pathways, J. Gen. Physiol., 1959, Vol 42: pp. 1037-1066.

As suggested by Fairchild and Sterman, sensory-motor feedback is an important element in the production of seizures. In the freely-moving animal of figure 1, for example, the first seizure was seen at 162 minutes, whereas in the paralyzed condition this cat did not show a seizure until 202 minutes (fig. 2), even though the dosage was twice as great. In practical terms this means that a person suffering exposure to UDMH should be kept as quiet as possible, as would be the case with other types of convulsants.

The paroxysmal neural activity due to UDMH poisoning appears to begin in the limbic system and then spreads to include the cerebral cortex. In this respect UDMH intoxication mimics the effects of temporal lobe epilepsy.

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